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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/284,009	04/05/1999	CLAIRE E. LEWIS	550-128	1771

7590 07/01/2004

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EXAMINER	
QIAN, CELINE X	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 07/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/284,009	LEWIS ET AL.	
	Examiner	Art Unit	
	Celine X Qian	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *87-93,101,104,109-116 and 120-125* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *87-93, 101, 104, 109-116, 120-125* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 April 1999* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 87-93, 101, 104, 109-116 and 120-125 are pending in the application.

This Office Action is in response to the Amendment filed on 4/8/04.

Response to Amendment

The objection to claim 123 has been withdrawn in light of Applicant's amendment of the claim.

The rejection of claims 109 and 110 under 35 U.S.C. 112 2nd paragraph has been withdrawn in light of Applicant's amendment of the claims.

The rejection of claims under 35 U.S.C.112 1st paragraph is maintained for reasons set forth of the record mailed on and further discussed below.

The rejection of claims 89-93 under 35 U.S.C. 112 2nd paragraph is maintained for reasons set forth of the record mailed on and further discussed below.

Claim 110 is rejected under 35 U.S.C. 112 2nd paragraph for reasons given below.

Response to Arguments

Claim Rejections - 35 USC § 112

Claims 87-93, 101, 104, 109-116 and 125 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a mononuclear phagocyte modified to comprise at least one regulatable element operably linked to at least one nucleotide sequence of interest (NOI), wherein said regulatable element is selected from a hypoxia regulatable element, an ischemic regulatable element and a stress regulatable element, and wherein the NOI is a marker gene or reporter gene; a delivery system comprising said mononuclear phagocyte; a construct comprises at least one regulatable element operably linked

to at least one nucleotide sequence of interest (NOI), wherein said regulatable element is selected from a hypoxia regulatable element, an ischemic regulatable element and a stress regulatable element, and wherein the NOI is a marker gene or reporter gene; and a method of internalizing said construct into a mononuclear phagocyte, does not reasonably provide enablement for such mononuclear phagocyte comprising a regulatable element selected from hypoxia, ischemic and stress element, operably link to any type of NOI. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

Claims 120-124 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In response to this rejection, Applicants argue that according to the case law *In re Marzocchi*, the Examiner fails to provide an objective reason to doubt the assumption of an enabling disclosure for the full scope of the claims. Applicants further argue that the specification adequately demonstrates the ability to express sufficient levels of marker genes, and the specification describes multiple instances where the "therapeutic gene" is used to generate an active metabolite which kills the transduced phagocytes as well as nearby tumor cells by the "bystander effect." Moreover, Applicants submitted a declaration by Stuart Naylor which provides additional discussion of how the instant application could be followed to adequately express a "therapeutic gene" under control of a hypoxia response element (HRE) to result in tumor cell death *in vivo*. Applicants assert that this declaration demonstrates that the results

described in the declaration proves that expressing a therapeutic gene *in vivo* under HRE is routine experimentation rather than undue experimentation. Applicants thus conclude that the claimed invention is enabled to the full scope by the instant specification.

Applicants' arguments have been fully considered but deemed unpersuasive. Contrary to Applicants' assertion, the unpredictability of achieving high and sustained level of expression of any therapeutic gene to exert a therapeutic effect *in vivo* is not a mere allegation, but based on the teaching of the prior art as discussed in detail in the office action mailed on 7/7/00 (see page 4). Briefly, as indicated by Verma et al., although hundreds of clinical trails of gene therapy have been conducted, there is no single outcome to point to as a success story. The major problems that have been encountered are 1) the delivery of altered genes, and 2) the inability to obtain a sustained expression of the desired protein in a specified location. (see Verma et al., Nature, Vol. 389 page 239, 5th paragraph). As such, being a new field, the amount of guidance necessary in the specification has to be very detailed in order to provide enablement. However, contrary to Applicants' assertion, the specification fails to teach any therapeutic effect *in vivo* by expressing a therapeutic gene by HRE in a mononuclear phagocyte. Mere statement as for generating constructs comprising therapeutic genes listed in Table 1 cannot predict the success of delivering and expressing the therapeutic gene in high and sustained level to achieve a therapeutic effect because of the art recognized technical difficulties. Applicants are invited to point to the detailed teaching in the specification regarding the alleged "multiple instances where the therapeutic gene is used to generate an active metabolite which kills the transduced phagocytes as well as nearby tumor cells by the bystander effect. Otherwise, the instant specification fails to provide an enabling disclosure to the full scope of the claims.

The declaration by Dr. Stuart Naylor discloses the construction of an adenoviral vector AP48c which comprises the cytochrome P4502B6 under the control of a HRE promoter, and the P450 reductase gene under the control of the CMV promoter. The declaration also discloses that this vector is transfected to macrophages. Further, the declaration discloses that administering macrophages transduced with said vector and CPA to a mouse ascitic ovarian cancer xenograft model prolonged survival of said mouse. The declaration also refers to Kluth et al. and Griffith et al. and asserts that the data provided in the declaration and in these references support that expressing a therapeutic gene is routine experimentation. Thus, the declaration concludes that the instant specification supports the full scope of the claims.

This declaration has been fully considered. However, it fails to provide enablement for the full scope of the invention. The claims encompass expressing any therapeutic gene in a mononuclear phagocyte as a pharmaceutical composition. To achieve high and sustained expression of a therapeutic gene sufficient to result a therapeutic effect *in vivo* is unpredictable because of the art-recognized difficulties as discussed above. The data provided by the declaration demonstrates the result of empirical experimentation, rather than routine experimentation, which does not extend the predictability of successful result would be achieved by other therapeutic gene. In addition, the Griffith reference cannot be relied on to support successful outcome *in vivo* since the experiments in the reference are conducted *in vitro* culture system. As discussed in the previous office action mailed on 11/21/03 (see page 4, bottom paragraph to page 5, 2nd paragraph), the Kluth and Nishihara references cannot be relied on to support the enablement of the claimed invention because they are published long after the

priority date of the instant specification. Therefore, the claims are not enabled for the full scope by the instant specification, and the rejection is maintained.

Claims 89-93 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In response to this rejection, Applicants argue that the binding location may be at a variety of places, and such broadness is not equivalent to indefiniteness. Applicants argue that the claims are not indefinite when properly read in light of the content of the specification (page 13, 14, 20-24), which teaches how binding agents can be incorporated into the mononuclear phagocytes. Applicants thus conclude that the claims are definite.

This argument has been fully considered but deemed unpersuasive. Although the specification gives light to the claims, the interpretation of the claim is not limited by the examples given in the specification. The claims recite "a binding agent capable of binding to a cell surface element of the mononuclear phagocyte." If the binding agent is located inside the cell, it is unclear how it can bind to the cell surface element of the mononuclear phagocyte. The claims may be broad, however, it must set metes and bounds so that the limitation can be interpreted clearly. Therefore, this rejection is maintained.

New Grounds of Rejection Necessitated by Applicant's Amendment

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 110 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "hypoxic, ischemic or stress site is a target site of a tumor associated condition" renders the claim indefinite because it is unclear what kind of target site Applicants are referring to. Does it mean the site is targeted by the tumor associated condition (the specification does not teach what sites are targeted by tumor associated condition), or the hypoxic, ischemic or stress site is associated with a tumor condition? Clarification is required.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 571-272-0777. The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Celine Qian, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER